

PATENT COOPERATION TREATY

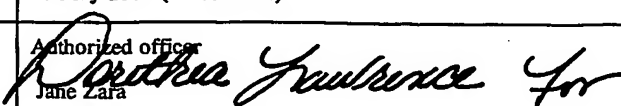
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 21 JUN 2004

WIPO PCT

Applicant's or agent's file reference ISIS0046-500	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US03/17638	International filing date (day/month/year) 04 June 2003 (04.06.2003)	Priority date (day/month/year) 04 June 2002 (04.06.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68; C12P 19/34; C12N 15/63; C07H 21/02, 21/04; A01N 43/04 and US Cl.: 435/6, 91.1, 91.31, 455, 458; 514/44; 536/23.1, 24.5		
Applicant ISIS PHARMACEUTICALS, INC.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u>0</u> sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 31 December 2003 (31.12.2003)	Date of completion of this report 26 May 2004 (26.05.2004)	
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer  Jane Zafa Telephone No. (703) 308-0196	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/17638

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-111 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☒ the claims:
pages 112 and 113, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.
- ☒ the sequence listing part of the description:
pages 1-90, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in printed form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/17638**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>1-20</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>15-20</u>	YES
	Claims <u>1-14</u>	NO
Industrial Applicability (IA)	Claims <u>1-20</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over YOKOYAMA et al. in view of MILNER et al and MCKAY et al. YOKOYAMA et al. teach the nucleotide sequence of the target sterol regulatory element binding protein-1 and its involvement in cholesterol metabolism in humans. MILNER et al teaches methods of designing and assessing antisense oligonucleotides for their ability to target and inhibit a target gene of known sequence in vitro. MCKAY et al teach methods and compositions comprising antisense oligonucleotides for targeting and inhibition of a target gene in cells in vitro, which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system for target cell delivery in vitro, and which antisense oligonucleotides further comprise phosphorothioate internucleotide linkage, 2'-O-methoxyethyl sugar and 5-methyl cytosine nucleobase modifications, as well as chimeric antisense. It would have been obvious to utilize the methods taught by MILNER to design and assess antisense targeting the nucleotide sequence encoding sterol regulatory element binding protein-1 in target cells in vitro. It would have been obvious to incorporate the modifications taught by MCKAY et al. into antisense to enhance stability and target binding of the antisense for optimizing target gene inhibition in vitro.

Claims 15-20 meet the criteria set out in PCT Article 33(2) and (3), because the prior art does not teach or fairly suggest methods of treating an animal having a disease or condition associated with sterol regulatory element binding protein-1 comprising the administration of antisense in vitro.

Claims 1-20 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.

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NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No. PCT/US03/17638	Applicant's or agent's file reference ISIS0046-500	Date of informal communication (day/month/year) 26 May 2004 (26.05.2004)
Applicant ISIS PHARMACEUTICALS, INC.		

<u>Communication</u> <input checked="" type="checkbox"/> by telephone <input type="checkbox"/> personal	<u>Participants</u> <div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> Identity checked <input type="checkbox"/> authorization checked <input type="checkbox"/> personally known </div> <input checked="" type="checkbox"/> Applicant: ISIS ,PHARMACEUTICALS, INC. <input checked="" type="checkbox"/> Agent: Quan Le Nguyen <input checked="" type="checkbox"/> Examiner(s): Jane Zara
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Summary of communication:

Applicants' representative authorized the International Preliminary Examination Report in lieu of the Written Opinion.

☐ An extension of time limit is granted (Form PCT/IPEA/427).

☒ A copy of this note is being sent to the applicant with Form PCT/IPEA/429.

PCT/IPEA/424.

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